

Management Strategies to Reduce Exacerbations in non-T2 Asthma



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1. To appreciate important pathways responsible for non-T2 airway inflammation in asthma.
2. To apply current and evolving management strategies to reduce exacerbations in patients with non-T2 asthma.

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There have been considerable advances in our understanding of asthmatic airway inflammation, resulting in a paradigm shift of classifying individuals on the basis of either the presence or the

absence of type 2 (T2) inflammatory markers. Several novel monoclonal antibody therapies targeting T2 cytokines have demonstrated significant clinical effects including reductions in

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Abbreviations used

AHR- Airway hyperresponsiveness
BT- Bronchial thermoplasty
CXCL- C-X-C motif chemokine ligand
DAMP- Damage-associated molecular pattern
ICS- Inhaled corticosteroid
T1- Type 1
T2- Type 2
T3- Type 3
TSLP- Thymic stromal lymphopoietin

acute exacerbations and improvements in asthma-related quality of life and lung function for individuals with T2-high asthma. However, there have been fewer advancements in developing therapies for those without evidence of T2 airway inflammation (so-called non-T2 asthma). Here, we review the heterogeneity of molecular mechanisms responsible for initiation and regulation of non-T2 inflammation and discuss both current and potential future therapeutic options for individuals with non-T2 asthma. © 2021 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2021;9:2588-97)

Key words: Asthma; Airway inflammation; Non-T2

INTRODUCTION

Asthma is a common condition, affecting more than 300 million people globally. It is now understood to be a heterogeneous disorder characterized by reversible airflow obstruction, airway hyperresponsiveness (AHR), and chronic airway inflammation. The primary goals of asthma management are to optimize symptom control, maximize lung function, and prevent acute exacerbations, which serve as the primary driver of asthma-related health care costs, morbidity, and mortality.¹ However, despite use of standard therapies such as inhaled corticosteroids (ICSs) and bronchodilators, 3% to 10% of individuals with asthma have disease that remains poorly controlled with frequent symptoms and acute exacerbations.²⁻⁴ Although some of this poor disease control is due to either suboptimal adherence or delivery of inhaled medications, many individuals with poorly controlled asthma have persistent symptoms despite appropriate medication use.

The concept of asthma heterogeneity dates to Rackemann,⁵ with the phenotypic division of asthma as either *extrinsic* (allergic) or *intrinsic* (nonallergic). Investigation of airway inflammation has proven critical to understanding the pathogenesis and, therefore, heterogeneity of asthma. By determining the distinct molecular mechanisms that can cause and regulate inflammation in asthma, personalized treatment approaches can reduce the multifaceted burdens of disease. Increasingly detailed cellular and molecular studies of airway inflammation have refined our understanding of asthma heterogeneity, and our current paradigm broadly dichotomizes asthmatic airway inflammation as type 2 (T2)-high versus non-T2 asthma. T2-high asthma is classically associated with eosinophilic airway inflammation and elevations in the T2 cytokines, IL-4, IL-5, and IL-13. Biomarkers for T2-high asthma include increased peripheral blood and/or sputum eosinophils as well as elevated

fraction of exhaled nitric oxide. IgE and allergen-specific IgE titers are also biomarkers but are less specific.⁶ The efficacy of novel T2-directed biologics provides convincing evidence that T2 inflammation plays a causal role for this subgroup of asthma and has indicated a particularly important role in the pathogenesis of exacerbations.⁷⁻⁹

In contrast, non-T2 disease only refers to the absence of features of T2-high asthma, clinically defined by low peripheral blood and sputum eosinophils as well as low fraction of exhaled nitric oxide (Figure 1). To date, a comprehensive and detailed understanding of the mechanisms of non-T2 asthma and its associated phenotypic and endotypic characteristics is lacking, but current evidence suggests that non-T2 asthma includes heterogeneous subgroups of airway inflammation. Insight into the clinical and phenotypic characteristics of non-T2 asthma is emerging: later onset of disease, diminished responsiveness to corticosteroids, and frequent exacerbations.^{3,4,10} Patterns of airway cellular inflammation that have been described in non-T2 asthma include neutrophilic and paucigranulocytic profiles.¹¹ However, the precise role of each inflammatory pathway observed in non-T2 asthma remains uncertain. The diversity, overlap, and heterogeneity of the inflammatory pathways present in this group has left clinicians without molecularly targeted therapeutics and thus with a more limited and empiric arsenal of treatment options for these individuals.

Here, we review the known mechanisms associated with non-T2 airway inflammation, as well as the current treatment options for individuals with non-T2 asthma. We also discuss novel therapeutics for non-T2 asthma currently under investigation.

MECHANISMS OF AIRWAY INFLAMMATION IN ASTHMA

T2 and non-T2 inflammation

Inflammation can be classified as type-1 (T1), type-2 (T2), and type-3 (T3) responses. Intracellular and acute threats (such as bacteria and viruses) are primarily addressed by T1 responses, whereas extracellular and chronic threats are addressed by T2 responses. A T3 response may occur with both intracellular and extracellular threats, especially in their chronic forms. Importantly, the above classification leaves out various forms of the innate immune response, which may involve macrophages/monocytes, neutrophils, and resident tissue cells.¹² In reality, many forms of the immune response coexist in disease states, but one form may dominate over others in a time and context-dependent manner. Such is the case with airway inflammation in asthma, and it should be noted that both T2 and non-T2 inflammation can coexist in individuals with severe disease.

T2 inflammation is driven by IL-4, IL-5, and IL-13, which can be produced by CD4⁺ T_H2 cells, type 2 innate lymphoid cells, natural killer cells, natural killer T cells, T follicular helper cells, mast cells, basophils, and, under some circumstances, macrophages and eosinophils.¹³ The concept of T2-high asthma was derived from the initial recognition of allergen-specific T_H2 cells and IgE-producing B cells as fundamental to airway inflammation in many individuals with asthma.¹⁴ Other cellular and molecular features of T2-high asthma classically include eosinophil and mast cell accumulation in the bronchial mucosa,¹⁵⁻¹⁷ elevation of IL-4, IL-5, and IL-13 in the airways,¹⁸ and changes in epithelial gene expression patterns in response to these cytokines.¹⁹ More recently, the cellular contribution to T2-high

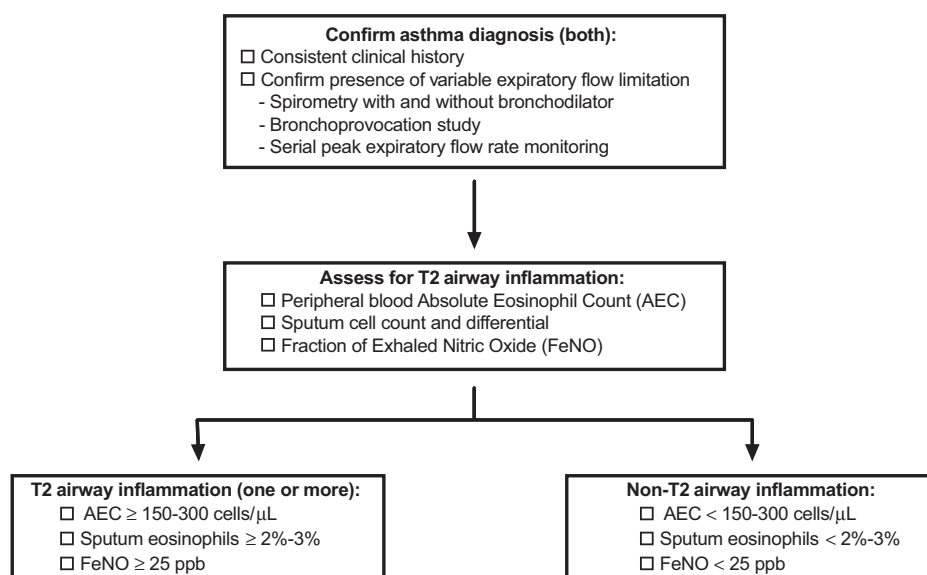


FIGURE 1. Suggested approach to asthma diagnosis and identification of T2 and non-T2 airway inflammation. *ppb*, Parts per billion.

asthma was recognized to include type 2 innate lymphoid cells^{20,21} and epithelial cell generation of thymic stromal lymphopoietin (TSLP), IL-25, and IL-33.²²⁻²⁵

Non-T2 asthma includes all forms of airway inflammation other than T2 inflammation, as well as noninflammatory drivers of AHR, such as abnormalities in neuronal signaling and airway smooth muscle (Figure 2). Given the classic association between T2-high asthma and eosinophilic airway inflammation, non-T2 asthma has also been defined as noneosinophilic airway inflammation. Histologically, non-T2 inflammation may be dominated by neutrophils, lymphocytes, macrophages, and/or inflammatory stromal cells, and both neutrophilic and paucigranulocytic patterns of airway cellular inflammation have been described in this asthma subgroup.¹¹ Here, we review the current evidence of T1, T3, and innate inflammation in asthma.

T1 inflammation in asthma

Numerous studies have implicated a role for ongoing T1 inflammation in asthma, including identification of increased levels of T1 cytokines such as TNF- α ²⁶ and IFN- γ ²⁷ in bronchoalveolar lavage fluid of some patients with asthma. Studies of populations with severe asthma have identified higher expression of *IFNG* and numbers of IFN- γ ⁺ cells in bronchoalveolar lavage samples²⁸ and discovered increased numbers of IFN- γ ⁺ staining cells in airway biopsies.²⁹ Transcriptomic analyses have also identified increased expression of multiple transcripts involved in T1 inflammation.³⁰⁻³² Despite evidence of ongoing T1 inflammation in some individuals with asthma, the trigger and ongoing source of this inflammatory response remains poorly understood. Viral infections induce T1 inflammation and are frequent triggers of acute asthma exacerbations, particularly rhinovirus and respiratory syncytial virus infections.³³ Although these infections are usually self-limited, there have been ongoing efforts to understand how these infections might promote chronic T1 inflammation in asthma. Infections trigger the release of damage-associated molecular patterns (DAMPs) such as host DNA,

nucleosomes, histones, and high-mobility group box 1, which could activate many DAMP sensors and sustain T1 inflammation.

T3 inflammation in asthma

The differentiation of T_H17 and type 3 innate lymphoid cells occurs under the influence of IL-1 β and IL-6.³⁴ The signature T3 cytokines, IL-17A and IL-17F, and the IL-17A-induced chemokines (C-X-C motif chemokine ligand [CXCL]1, CXCL2, CXCL7, CXCL8) can be elevated in asthma, especially in asthmatic individuals with neutrophilic airway inflammation.³⁵ IL-17A and IL-17F stimulate secretion of chemokines and growth factors to induce neutrophilic inflammation and tissue regeneration. Although some investigators have reported a correlation between IL-17A and neutrophilic asthma,³⁶ others have failed to detect an association.³⁷ It should also be noted that the T3-inducing cytokines IL-1 β and IL-6 can directly induce neutrophilic inflammation as an innate response independent of a T3 immune response as observed in autoinflammatory inflammasomopathies.³⁸

Innate inflammation in asthma

Phagocytes such as macrophages, monocytes, and neutrophils as well as tissue cells (epithelial cells, fibroblasts, and smooth muscle cells) can directly respond to infection and environmental toxicants. These cells can generate a plethora of proneutrophilic cytokines/mediators/DAMPs, which include IL-1 α , IL-1 β , IL-6, IL-33, TNF- α , CXCL1, CXCL2, CXCL7, CXCL8, GM-CSF, G-CSF, pentraxins (including C-reactive protein), serum amyloid A proteins, S100A proteins, antimicrobial peptides (cathelicidins, defensins), leukotrienes (including leukotriene B₄), prostaglandins, and other lipid mediators (eg, platelet-activating factor).^{39,40} The foregoing mediators trigger neutrophilic infiltrates, tissue damage, and other features of inflammation. Several of these mediators are elevated in non-T2 asthma.⁴¹⁻⁴⁵

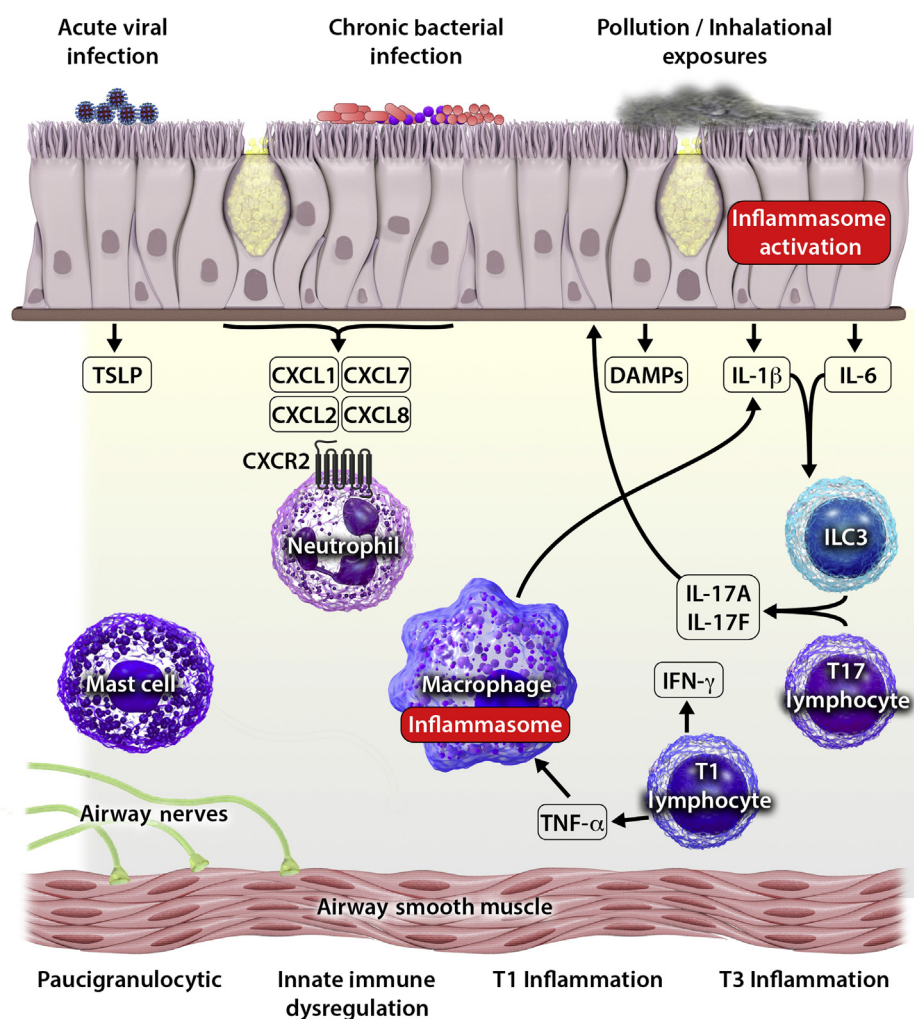


FIGURE 2. Mechanisms of non-T2 airway inflammation in asthma. *CXCR2*, C-X-C motif chemokine receptor 2; *ILC3*, type 3 innate lymphoid cell.

Potential mechanisms for induction of T3 and innate inflammation in asthma

Infection and dysbiosis. An increasing body of literature suggests that chronic low-grade bacterial infection of the airways may contribute to uncontrolled asthma in a subgroup of individuals,^{42,44,46} with some studies reporting that 40% of patients with refractory asthma have culture positive bacterial infection.^{42,45} Pathogens include common respiratory strains such as *Staphylococcus*, *Streptococcus*, *Haemophilus*, and *Moraxella*, as well as uncommon strains such as *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Pseudomonas*.^{42,44-46} Colonization of the oropharynx with *Streptococcus*, *Haemophilus*, and *Moraxella* in neonates is associated with development of childhood asthma⁴⁷ and low-grade systemic inflammation.⁴⁸ Similarly, presence of *Moraxella* or *Haemophilus* species in the sputum has been associated with severe asthma and sputum neutrophilia, as has low microbial diversity.⁴⁹⁻⁵¹

Environmental toxicants and air pollution. Air pollution has been associated with neutrophilic airway

inflammation and severe asthma.^{52,53} The association has been demonstrated for PM_{2.5}, ozone, nitrogen oxide, sulfur dioxide, traffic-related air pollution (eg, diesel exhaust) as well as particle-depleted air pollution. Some of the postulated mechanisms include oxidative cellular stress injury,⁵⁴ leading to the induction of inflammasome, innate, and T3 immune responses.⁵⁵

Inflammasome dysregulation. Inflammasomes generate mature IL-1β and IL-18 through caspase 1. Transcriptomic studies of sputum samples have shown increased expression of inflammasome-associated molecules among patients with asthma with higher sputum neutrophil counts.^{52,56-58} In agreement, multiple studies demonstrated increased IL-1β in sputum^{56,57} and bronchoalveolar lavage^{41,42,44,47} from patients with neutrophilic asthma. Inflammasomes function downstream of other known triggers of neutrophilic asthma, including infection, environmental toxicants, and DAMPs, and thus could play an important role in neutrophilic asthma.

TABLE I. Potential management strategies for non-T2 asthma

Nonpharmacologic interventions	
Smoking cessation	Recommended for all patients. Smoking cessation is associated with improved lung function and disease control
Weight loss in obese patients	Surgical and nonsurgical weight loss strategies improve lung function and asthma quality of life, and reduce exacerbation frequency
Bronchial thermoplasty	ERS/ATS and GINA recommend undergoing BT only as part of a clinical trial or registry. NAEPP recommends against BT, but acknowledges it can be considered for select patients
Pharmacologic interventions	
Current therapies to consider	
Chronic macrolide therapy	ERS/ATS and GINA recommend use for select patients with severe asthma. Avoid use in patients with dysrhythmias and use with caution in patients with hearing loss. Risk of inducing antimicrobial resistance
Long-acting muscarinic antagonist	ERS/ATS, GINA, and NAEPP recommend use for select patients with asthma not controlled with ICS-LABA
Selected future therapies under investigation	
Targeting TSLP	Results are pending from 2 phase 3 clinical trials using tezepelumab in severe asthma (NCT03347279, NCT03406078)
Targeting IL-17	Results are pending from a phase 2 clinical trial of CJM112 (anti-IL-17A) in severe asthma (NCT03299686)
Targeting IL-6	Phase 2 clinical trial using clazakizumab (anti-IL-6) in severe asthma is currently enrolling (NCT04129931)
Targeting mast cells	Phase 2 clinical trial using imatinib (c-KIT inhibitor) in severe asthma is currently enrolling (NCT04129931)

ATS, American Thoracic Society; ERS, European Respiratory Society; GINA, Global Initiative for Asthma; NAEPP, National Asthma Education and Prevention Program.

Non-T2 paucigranulocytic asthma

The mechanism of this form of asthma is largely unknown. Increased expression of mitochondrial oxidative stress-related genes was reported in paucigranulocytic non-T2 asthma.³² Mast cell interactions with the airway epithelium,¹⁷ airway smooth muscle,⁵⁸⁻⁶⁵ and airway nerves⁶⁶⁻⁷⁵ may play a role in regulating AHR.

MANAGEMENT OF NON-T2 ASTHMA

The clinical symptomatology of asthma is nonspecific, and thus it is critical to confirm the diagnosis, particularly in individuals with poorly controlled symptoms despite standard asthma therapies. Symptoms related to cardiovascular disease, upper airway disease, and other primary lung diseases can be incorrectly diagnosed as asthma, which highlights the importance of objectively demonstrating variable airflow obstruction and/or airway hyperresponsiveness.⁷⁶ Similarly, individuals with asthma often have comorbid disease processes or exposures that either mimic symptoms of asthma or contribute to ongoing airway inflammation and require concurrent management, including rhinosinusitis, gastroesophageal reflux disease, obstructive sleep apnea, obesity, inducible laryngeal obstruction, and inhalational exposures.

Confirming the presence or absence of T2 airway inflammation is essential in the current era of asthma management. Presently, there are no reliable biomarkers for individuals with non-T2 asthma, and thus, clinicians must largely rely on the persistent absence of T2 biomarkers to identify these individuals. However, previous studies have suggested that measuring sputum cell counts for isolated neutrophilia may be helpful,⁷⁷ and there is ongoing work to specifically identify markers of

neutrophilic airway inflammation, including assessment of exhaled volatile organic compounds.⁷⁸

Here, we review the nonpharmacologic and pharmacologic treatment options for individuals with non-T2 asthma (Table I). However, before starting additional pharmacotherapy, it is critical to ensure the basic tenets of asthma management have been optimized, including inhaler technique, treatment adherence and self-management skills, and identification and management of comorbid conditions. Providers should also reassess the dose of ICS in these patients, because many are already established on high ICS doses and it has become clear that further intensification of ICS treatment is ineffective in this population.⁷⁷ High-intensity ICS may result in overall harm in individuals without corticosteroid-responsive pathology, perhaps by favoring airway infection.⁷⁹ Although deescalation of ICS therapy can be challenging in highly symptomatic patients, there is a strong suggestion that individuals with non-T2 asthma benefit from biomarker-directed downtitration of corticosteroids.^{80,81}

Nonpharmacologic interventions

Smoking cessation. Smoking cessation is indicated for all individuals with asthma regardless of underlying health conditions and may be particularly important in managing neutrophilic inflammation in non-T2 asthma. Smoking worsens asthma symptoms^{82,83} and is associated with decreased responsiveness to inhaled and oral corticosteroids.^{84,85} Previous studies have identified associations between active cigarette smoking and sputum neutrophilia in asthma,^{86,87} and one study discovered increased neutrophils and IL-17A⁺ staining cells in the bronchial mucosa of endobronchial biopsies from asthmatic smokers.⁸⁸ Smoking cessation is associated with improved lung function and disease

control,⁸⁹⁻⁹¹ with one study demonstrating reduced sputum neutrophilia in patients with asthma who successfully quit smoking.⁸⁹

Weight loss in individuals with obesity. Obese individuals with asthma are a heterogeneous group,⁹² and studies have discovered evidence of both T2⁹³ and non-T2 airway inflammation^{94,95} in these individuals. There have been several studies demonstrating that mechanical factors associated with excess adipose tissue play a key role in driving AHR in this population.⁹⁶⁻⁹⁸ Weight reduction strategies with either nonsurgical⁹⁹ or surgical^{100,101} approaches have been shown to improve lung function and asthma-related quality of life, and reduce the frequency of exacerbations. The mechanism by which weight reduction results in improved asthma control remains unclear, but, regardless of asthma type, both surgical and nonsurgical weight loss strategies can provide benefit for morbidly obese individuals.

Bronchial thermoplasty. Bronchial thermoplasty (BT) is a bronchoscopic procedure in which thermal energy is delivered via a radiofrequency generator to impact airway remodeling.¹⁰² The precise mechanism of how this intervention improves asthma control remains unclear, but studies have demonstrated reduction in airway smooth muscle mass as well as ablation of airway nerve fibers, both of which may reduce AHR.^{103,104} The effect of BT on the airway epithelium remains unclear.¹⁰⁵ There is considerable literature demonstrating the long-term safety of this intervention¹⁰⁶ and its ability to reduce the frequency of emergency department visits and severe exacerbations.¹⁰⁷ However, although several professional societies have endorsed the use of BT for carefully selected patients, the most recent iterations of the International European Respiratory Society/American Thoracic Society guidelines on severe asthma and the Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma recommend undergoing BT only in the context of a clinical trial or registry.^{1,108} The most recent National Asthma Education and Prevention Program focused updates on asthma management recommend against BT but acknowledge that it can be considered for selected patients and similarly suggest that BT be offered in the setting of a clinical trial or registry.¹⁰⁹

Pharmacologic interventions

New drug discovery in airways disease has a high failure rate, and there is often concern that the effects of a potentially efficacious drug have been masked or diluted because of poor patient stratification. This issue is particularly relevant to non-T2 asthma in which the heterogeneity of airway inflammation and key outcome measures (ie, exacerbations) are incompletely understood. Here, we review established guideline-recommended treatments likely to be effective in non-T2 asthma and discuss several investigational approaches that are currently in clinical trial development.

Chronic macrolide therapy. Several studies have demonstrated benefit for long-term use of macrolide antibiotics in asthma.¹¹⁰⁻¹¹² The largest interventional study was a randomized, double-blind, placebo-controlled parallel group trial that demonstrated improvement in asthma quality-of-life scores and found a 40% reduction in asthma exacerbations, which was seen in both eosinophilic and noneosinophilic phenotypes (defined by sputum eosinophils <3% or, if sputum samples were

unavailable, then peripheral blood eosinophils <300 cells/ μ L).¹¹² Azithromycin has many potentially relevant antibacterial, antiviral, and anti-inflammatory effects. However, it is likely that an effect on *Haemophilus influenza* infection and/or colonization is most responsible for the beneficial effects in asthma because a *post hoc* analysis suggested those with highest *H influenzae* abundance derived the most benefit from azithromycin therapy in terms of exacerbation reduction.^{113,114} Macrolides are recommended in current European Respiratory Society/American Thoracic Society and Global Initiative for Asthma guidelines for selected adults with severe asthma but are not specifically discussed in the most recent National Asthma Education and Prevention Program guidelines. They have the potential for causing QT prolongation and hearing loss, but the greatest concern is inducing drug resistance in undiagnosed nontuberculous mycobacterial infection, making subsequent treatment difficult. A screening electrocardiogram should be performed in all patients before initiating treatment, and chronic macrolide therapy should be avoided in patients with a history of cardiac arrhythmia. Providers should exercise caution in starting chronic macrolide therapy in patients with baseline hearing loss.

Long-acting muscarinic antagonists. Several high-quality trials have investigated the addition of long-acting muscarinic antagonists to ICS/long-acting beta-agonist treatment, predominantly in severe asthma, leading to their inclusion as a step 4 or 5 option in current Global Initiative for Asthma guidelines.^{1,115-120} Tiotropium, glycopyrronium, and umeclidinium improve FEV₁ and asthma symptoms, but these effects are modest.^{116,121,122} There is less consistent evidence on the effect of long-acting muscarinic antagonists on exacerbations. Unlike higher ICS doses, the beneficial effects of long-acting muscarinic antagonists are independent of biomarkers of T2 airway inflammation, suggesting that they may be particularly applicable in non-T2 asthma.¹²³⁻¹²⁵

Novel pharmacologic therapies

Targeting TSLP. Tezepelumab, a humanized monoclonal antibody (mAb) that binds and neutralizes the epithelial alarmin TSLP, has been shown in a phase 2 study to reduce exacerbations in individuals with non-T2 asthma by approximately 40%.¹²⁶ Importantly, non-T2 asthma was defined by either a total IgE less than or equal to 100 IU/mL or peripheral blood eosinophil count less than 140 cells/ μ L, but there was a similar reduction in exacerbation frequency in patients with low fraction of exhaled nitric oxide (<24 ppb). However, there were no improvements in lung function or asthma symptoms in this group despite clear improvement in these outcomes in individuals with T2-high asthma. Previous studies have not demonstrated an effect of novel mAbs targeting T2 cytokines on exacerbation frequency in non-T2 asthma. Although the primary efficacy of tezepelumab is presumably driven by blocking the effects of TSLP and subsequently modulating the T2 immune response, these results suggest that tezepelumab may also inhibit a mechanism responsible for asthma exacerbations independent of T2 inflammation. One possibility is specific inhibition of mechanisms driving exacerbations related to acute viral infection.

Targeting neutrophilic inflammation. Neutrophilic inflammation appears to play a prominent role in a subset of individuals with non-T2 asthma, who may represent a

subpopulation with a distinct and targetable molecular pathway. IL-17 is important in recruiting neutrophils and has been associated with neutrophilic asthma, but studies of mAbs targeting IL-17 have been disappointing.¹²⁷ Brodalumab, an anti-IL-17 receptor A mAb, overall had no effect on asthma control in individuals with uncontrolled moderate to severe disease despite the use of ICS. Importantly, this study was performed in a general and unselected population, and the efficacy of anti-IL-17 therapy in non-T2 asthma, specifically in individuals with evidence of neutrophilic inflammation, remains unknown. Results of a recently completed phase 2 clinical trial of CJM112, an anti-IL-17A mAb, in individuals with asthma with low peripheral blood eosinophils and IgE levels may provide additional insights (NCT03299686).

Inhibition of neutrophil trafficking in response to IL-8 by blocking the C-X-C motif chemokine receptor 2 has been assessed in asthma. A small-molecule C-X-C motif chemokine receptor 2 antagonist markedly reduced sputum neutrophil counts in individuals with severe neutrophilic asthma¹²⁸ and was associated with reduced frequency of mild exacerbations. However, a larger trial with varying doses of a C-X-C motif chemokine receptor 2 antagonist in a population with severe asthma demonstrated no effect on exacerbations, lung function, or asthma control.¹²⁹ It is important to note that although this larger trial attempted to exclude patients with suspected T2-high eosinophilic asthma (defined as a peripheral blood eosinophil count of >500 cells/ μ L), this likely resulted in inclusion of some patients with eosinophilic airway inflammation in the study population. There was also no direct assessment for neutrophilic airway inflammation. Thus, a potentially important signal could have been lost because of poor patient stratification.

Targeting IL-6. Previous studies have identified higher serum IL-6 levels in individuals with asthma,¹³⁰ and genomic studies have demonstrated associations between IL-6-related genes and asthma.¹³¹ More recently, a study identified a subgroup of individuals with moderate to severe asthma and raised serum IL-6 levels, who were more likely to be obese, have more severe symptoms, higher frequency of exacerbations, and worse lung function.¹³² These findings provide reasonable rationale for evaluating anti-IL-6 therapies in a subset of individuals with severe asthma. Plasma IL-6 or the closely related and more clinically accessible biomarker C-reactive protein might be a useful predictive biomarker. Definitive trials are awaited with interest.

Targeting mast cells. Mast cells have been implicated as key effector cells in asthma, and their interactions with the airway epithelium and airway smooth muscle may play an important role in regulating AHR^{17,133} and airway inflammation.^{17,134,135} Imatinib induces mast cell apoptosis by inhibiting KIT proto-oncogene receptor tyrosine kinase and was recently shown to be effective in improving lung function, decreasing AHR, and reducing airway mast cells in individuals with severe asthma.¹³⁶ Secondary analyses revealed that improvement in lung function correlated with baseline airway neutrophil counts and that the effects on AHR were negatively correlated with baseline peripheral eosinophil counts, suggesting that imatinib may provide benefit to individuals with non-T2 asthma. Imatinib is being further studied in a phase 2 clinical trial for individuals with severe asthma (NCT04129931).

CONCLUSIONS

Non-T2 airway inflammation encompasses a heterogeneous group of inflammatory pathways including T1 and T3 immune responses as well as dysregulation of the innate immune system. Preliminary studies have suggested a role for respiratory viral infections in triggering a sustained T1 immune response, and additional studies have suggested a role for chronic bacterial infection or disruption of the airway microbiome, inhalation of environmental pollutants, and inflammasome dysregulation in driving T3 inflammation and ongoing activation of the innate immune system. Although there are some early studies attempting to identify novel non-T2 biomarkers, clinicians must rely on the sustained absence of classic T2 biomarkers to identify individuals with non-T2 asthma. Initial management strategies for individuals with poorly controlled symptoms should focus on confirming a diagnosis of asthma, optimizing inhaled medication delivery and adherence, and recognizing and managing relevant comorbid diseases. Providers are encouraged to reevaluate the role of higher doses of ICS in this patient population and potentially de-escalate steroid therapy. For individuals who remain with poor disease control, there is a reasonable body of evidence supporting the role of several nonpharmacologic and pharmacologic interventions, and there are ongoing studies evaluating the role of novel targeted therapeutics in specific patient subgroups. Despite these advances, management of non-T2 asthma remains challenging. Ongoing studies using systems biology approaches may better define this heterogeneous population and allow for more precise application of targeted therapeutics.

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